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(54) Extended release pharmaceutical formulations.

(57) An extended release pharmaceutical formulation adapted to approach zero order release of drug over a 12 to at least 24 hour period, comprised of a mixture of 0 to about 50% of an immediate release particle containing a drug, inert substrate and binder, coated with talc and up to 100% of an extended release particle comprising the immediate release particle coated with a dissolution modifying system containing plasticizers and a film forming agent.

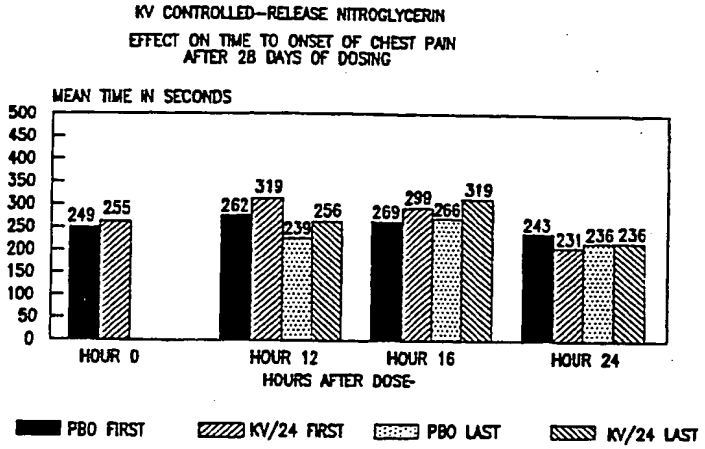

FIG. 1

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DeNEALE et al. (4,309,404) except that the core contains 20 to 70% drug, 30 to 72% of a mixture of a water-soluble polymer such as hydroxypropylmethylcellulose or hydroxypropylcellulose and water-insoluble polymer (ethylcellulose alone or in admixture with carboxypolymethylene, hydroxypropylcellulose and the like).

Each of the DeNEALE et al. and GULEY et al. patents disclose that their compositions provide substantially zero order release of the core containing drug for about 12 hours following the first hour of administration. Thus, zero order release is only obtained after the initial surge of release of drug in the first hour.

U.S. Patent 4,259,314 to LOWEY discloses a controlled long-acting dry pharmaceutical composition which includes a dry carrier formed from a mixture of hydroxypropylmethylcellulose (viscosity of 50 to 4000 cp in 2% aqueous solution at 20° C) and hydroxypropylcellulose (viscosity of 4000 to 6500 cp for a 2% aqueous solution at 25° C) which dry carrier is employed with a therapeutic agent such as aspirin, ascorbic acid and nitroglycerin.

U.S. Patent 4,610,870 to JAIN et al. discloses a controlled release pharmaceutical formulation which approaches zero order release of active drug, which is provided preferably in the form of a coated tablet, containing a core portion from which medicament, such as procainamide hydrochloride, is slowly released over a controlled length of time. The core also includes one or more hydrocolloid gelling agents having a viscosity of within the range of from about 10,000 to about 200,000 centipoises in 2% solution at 20° C, such as hydroxypropylmethylcellulose and/or methylcellulose, one or more non-swellable binders and/or wax binders (where the medicament and/or hydrocolloid gelling agents are non-compressible), one or more inert fillers or excipients, one or more lubricants, and optionally one or more antiadherents such as silicon dioxide and water.

Enteric-coated preparations are also referred to as another type of sustained release preparation. The release of the drug from an enteric-coated preparation is delayed by providing a coating layer soluble only after arrival at the intestine, that is after the pharmaceutical preparation passes through the stomach, and the extent of this delay is determined by the rate at which the pharmaceutical preparation is generally discharged from the stomach into the intestine. By combining an enteric portion with a usable portion soluble in the stomach, the release of the drug can be rendered continuously.

U.S. Patent 4,695,467 to UEMURA et al. relates to a sustained release tablet which comprises easily disintegrable granules containing (a) a drug, (b) a disintegrating agent selected from the group consisting of starch derivatives, gums, cellulose derivatives and ion-exchange resins, and (c) a water-soluble polymer selected from the group consisting of cellulose derivatives, synthetic water soluble polymers and polysaccharides, the surfaces of which granules are treated with a wax selected from the group consisting of plant or animal wax, hydrogenated oils and paraffin.

SUMMARY OF THE INVENTION

In accordance with the present invention, an extended release pharmaceutical formulation is prepared which is capable of approaching zero order release of drug over a 12 to at least 24 hour period. The formulations of the present invention are composed of a mixture of 0 to 50% of an immediate release particle containing a core of drug, inert spherical substrate particles and binder, coated with talc and up to 100% of an extended release particle comprising the immediate release particle coated with a dissolution modifying system containing plasticizers and a film forming agent, wherein the particle size of the extended release formulation is -10 + 60 mesh.

The drugs used in the formulations of the invention may be selected from a wide variety of pharmaceutical formulations with particular pharmaceutical compounds being analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system (CNS) drugs, metal salts, minerals, vitamins and mixtures thereof.

Another embodiment of the invention involves a process for preparing an extended release pharmaceutical formulation for oral administration which comprises:

a) forming a core material by spraying a solvent containing a dissolved binder onto a mixture of at least one drug and inert spherical substrate particles;

b) drying the resulting mixture to form a core material and coating the core material with talc;

c) coating the immediate release particles by spraying the particles with a dissolution modifying system containing plasticizer and film forming agent to form an extended release pharmaceutical formulation; and

A wide variety of medicaments which are orally administered both in tablet, capsule and particulate form may be used to prepare the particles according to this invention. These include drugs from all major categories, and without limitation, for example, analgesics, such as acetaminophen, ibuprofen, flurbiprofen, ketoprofen, voltaren (U.S. Patent 3,652,762), phenacetin and salicylamide; anti- inflammatories selected from the group consisting of naproxen and indomethacin; antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate, diphenhydramine hydrochloride, promethazine, brompheniramine maleate, dexbrompheniramine maleate, clemastine fumerate and triprolidine; antitussive selected from the group consisting of dextromethorphan hydrobromide and guaifenesin; expectorants such as guaifenesin; decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine; narcotics, such as morphine, and codeine and their derivatives, such as oxycodone and hydromorphone; antibiotics such as erythromycin, penicillins and cephalosporins and their derivatives; bronchodilators such as theophylline, albuterol and terbutaline; cardiovascular preparations such as diltiazem, propranolol, nifedepine and clonidine, and organic nitrates such as nitroglycerin, isosorbide 5-mononitrate and isosorbide dinitrate; central nervous system drugs such as thioridazine, , diazepam, meclizine, ergoloid mesylates, chlorpromazine, carbidopa and levodopa; metal salts such as potassium chloride, and lithium carbonate; minerals selected from the group consisting of iron, chromium, molybdenum and potassium; and vitamins selected from water-soluble vitamins such as B complex, vitamin C, vitamin B12 and folic acid.

Particularly preferred dosage forms involve use of pseudoephedrine hydrochloride; pseudoephedrine hydrochloride and chlorpheniramine maleate; and phenylpropanolamine hydrochloride and chlorpheniramine maleate, all of which have been found to exhibit the following dissolution ranges:

Hour 1	0 - 50%
Hour 8	50 - 80%
Hour 12	NLT 65%

It should be recognized that these drugs are representative and are not intended to limit the scope of the invention. The drugs are employed in amounts to provide a therapeutically effective dose and are preferably present in amounts of about 4 to about 85% by weight of the final formulation, and most preferably from about 40 to about 55% by weight.

When small amounts of a particular drug are used, that is amounts below about 50 mg per dosage form, (either alone or in combination with other drugs) it is advantageous to employ an optional carrier to aid in uniformly distributing the drug throughout the dosage form. Such carriers assist in bulking the drug to make it easier to be applied to the inert substrate. Exemplary carriers include sugar, lactose, gelatin, starch, and silicon dioxide. When employed, they are present in amounts of about 0.01 to about 15% by weight of the final product.

The immediate release particle core additionally contains an inert spherical substrate particle which aids in the diffusion/release of the drug from the formulation. The inert spherical substrate particles should be of the same general size so that the rate of drug release is not variable. In general, smaller particles result in rapid diffusion of drug, whereas larger particles result in a delay of drug diffusion. Suitable materials may be selected from sugar spheres and other substances which would not modify the drug release pattern or be reactive with the active component, such as non-toxic plastic resin beads. The inert spherical substrate particles are employed in the core of the immediate release particles in amounts of about 15 to about 40% by weight, and preferably in amounts of about 20 to about 35% by weight of the total formulation.

The drug adheres to the inert spherical substrate particle through a binding agent which is preferably applied by a suitable solvent. Water is the preferred solvent for water-soluble binders, whereas organic solvents are used with organic soluble binders. Binders may be selected from a wide range of materials such as hydroxypropylmethylcellulose, ethylcellulose, or other suitable cellulose derivatives, povidone, acrylic and methacrylic acid co-polymers, or pharmaceutical glaze. Exemplary solvents are water, ethanol, isopropyl alcohol, methylene chloride or mixtures and combinations thereof.

The binders are generally employed in small amounts which are just suitable to retain the drug on the inert spheres. Useful amounts may vary from about 0.5 to about 4% by weight, and preferably from about 1 to about 2% by weight of the total formulation.

The binder is preferably applied to the drug and inert spherical substrate in solution form. This may be achieved by dissolving the binder in either water or a suitable organic solvent such as isopropyl alcohol. When used as a solution, the solution generally contains from about 2 to about 25% binder and remainder

aid in offering various advantages. First, they assist in making hard granules which improves the binding characteristics of the matrix. Secondly, the particle size effects the final product particle size which can greatly influence the rate at which the polymer hydration or gel formation occurs in the capsule, tablet or particle surface. In general, particle sizes outside the ranges disclosed herein are unsuitable for preparing an extended release pharmaceutical formulation.

By employing the formulations of the invention, one is able to achieve an extended release system which is a dynamic system composed of wetting, hydrating and dissolution components. At the same time, other soluble materials or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials will be held in place until the surrounding encapsulation layer, erodes or dissolves away.

The extended release pharmaceutical formulations of this invention exhibit dissolution patterns which result in the reduction of various side effects associated with the normal use of such drugs. For example, cough/cold formulations containing pseudoephedrine hydrochloride are known to cause central nervous system disorders, such as enhanced agitation and insomnia. Such formulations when used according to the invention show significantly reduced side effects. In the case of potassium chloride which is a known gastrointestinal irritant, such irritation is significantly reduced when the metal salt is administered using the system of this invention. These same unexpected advantages would be expected to occur with the other pharmaceutical drugs and materials that are useful herein.

The extended release pharmaceutical formulation of the present invention may be comprised of two main components: the immediate release particles and extended release particles. The immediate release particles and extended release particles may be blended together and filled into hard gelatin capsules or formed into tablets with standard equipment.

A particularly preferred extended release pharmaceutical formulation according to the invention is comprised of a mixture of:

a) 0 to about 50% of an immediate release particle containing about 15 to about 40% by weight inert spherical substrate particle, about 0.5 to about 4% binder and about 4 to about 75% of at least one drug and a coating comprising about 4 to about 20% talc; and

b) up to 100% of an extended or controlled release particle comprising an immediate release granule of a) coated with a dissolution modifying system comprising about 0.5 to about 25% film forming agent, about 0.01 to about 5% plasticizer and up to 25% modifying agent, all percents herein are by weight of the final product.

Batch sizes may vary depending on the capacity and type of equipment used. Quantities of ingredients likewise can be varied with specified ranges to assure that the product meets the desired dissolution and potency characteristics. The following procedure describes one set of conditions and is not intended to be limiting thereto.

Another preferred controlled-release pharmaceutical formulation according to the invention uses an organic nitrate formulation for once-per-day oral administration which achieves a therapeutically effective level of the drug at least one organic nitrate, while effecting a drug holiday towards a latter portion of the daily dosing period so as not to induce tolerance.

Any organic nitrate within reason for treating a human mammal may be utilized in the formulation. Preferably, the organic nitrate is nitroglycerin, isosorbide 5-mononitrate, isosorbide dinitrate, or mixtures thereof. Furthermore, the organic nitrate may be in the form of a triturate with lactose and/or mannitol. For example, the nitroglycerin triturate can include 1-20 percent by weight nitroglycerin, the isosorbide 5-mononitrate triturate can include about 5-100 percent by weight isosorbide 5-mononitrate, and the isosorbide dinitrate triturate can include about 1 to 90 percent by weight isosorbide dinitrate.

The rate of release of the organic nitrate formulation may be described according to standardized dissolution testing procedures. In this regard, when the organic nitrate is nitroglycerin, the rate of release of the nitroglycerin from the formulation in substantially equivalent to a rate of release of the nitroglycerin as measured in vitro in a basket assembly according to U.S. Pharmacopoeia XXI, wherein less than 30% of the nitroglycerin is released after 1 hour of measurement, less than 40% of the nitroglycerin is released after 12 hours of measurement, and less than 90% of the nitroglycerin is released after 24 hours of measurement. When the organic nitrate is isosorbide 5-mononitrate triturate, the rate of release of the isosorbide 5-mononitrate is substantially equivalent to a rate of release of the isosorbide 5-mononitrate as measured in vitro according to dissolution testing in accordance with U.S. Pharmacopoeia XXI Apparatus II, paddle method, in a 7.5 pH phosphate buffer, wherein less than 30% of the isosorbide 5-mononitrate is released after 1 hour of measurement, less than 65% of the isosorbide 5-mononitrate is released after 4 hours of measurement, less than 90% of the isosorbide 5-mononitrate is released after 12 hours of measurement. When the organic nitrate is isosorbide dinitrate, the rate of release of the isosorbide dinitrate is substantially equivalent to a rate of release of the isosorbide dinitrate as measured in vitro according to dissolution

the drug efficacy sought. When administered in proper dosage forms, the formulations are able to deliver the drugs in zero order release rates to achieve from about 12 to 24 hours drug delivery.

Additionally, the invention is directed to a method of treating mammals, including man, by the once-per-day oral administration of the drug by orally administering once during each 24 hour time period a controlled-release formulation. When using an organic nitrate for example, the film forming polymer permits release of the organic nitrate from the formulation, over a daily dosing period, at a rate that achieves a therapeutically effective level of the organic nitrate, while effecting a drug holiday towards a latter portion of the daily dosing period so as not to induce tolerance.

The treating of the human mammal may be for the treatment of congestive heart failure, systemic hypertension, pulmonary hypertension, cardiomyopathic heart, valvular heart disease, vasospastic disease, congenital heart disease, or esophageal spasms. Relating to this, clinical studies have shown that the product is therapeutically efficacious, preventing or delaying the onset of chest pain for at least eighteen hours after a single daily dose.

The present invention is further illustrated by the following examples. All percentages used throughout the specification and claims are based on the weight of the final product, unless otherwise indicated, and all formulations total 100% by weight.

EXAMPLE 1

PSEUDOEPHEDRINE HYDROCHLORIDE 240 mg EXTENDED-RELEASE CAPSULE	
Composition	%
Pseudoephedrine Hydrochloride, USP	45.28
Sugar Spheres, NF	15.12
Talc, USP	15.32
Povidone, USP	0.35
Pharmaceutical Glaze, NF	1.80
Calcium Stearate, NF	3.08
Ethylcellulose, NF	1.55
Diethyl Phthalate, NF	0.02
Sugar Spheres, NF-QS	17.48
	100.00

The pseudoephedrine hydrochloride is pulverized and applied on the sugar spheres using 0.178 cc/capsule of a solution comprised of 31.8% v/v 2 lb. cut pharmaceutical glaze (prepared by diluting 4 lb. cut pharmaceutical glaze with an equal volume of isopropyl alcohol), 13.6% v/v 10% povidone solution in isopropyl alcohol, 9.1% v/v water, 45.5% v/v isopropyl alcohol.

The so prepared particles are dried to remove the residual solvents at temperatures up to 80° C.

To these dried particles, an inert seal coat of 32.18 mg of talc with 0.025 cc/capsule of the same solution as used for the application of the pseudoephedrine hydrochloride is applied. After the inert seal is applied, the particles are dried again to remove any residual solvents at varying temperatures up to 80° C.

To the above particles the diffusion control membrane is applied. The solution of this membrane is composed of 5% w/w ethylcellulose with 0.1% w/w diethyl phthalate in a co- solvent system composed of 2 parts of isopropyl alcohol and 1 part methylene chloride, applied with 49 mg of talc and the calcium stearate. The so prepared particles are dried to remove any residual solvents at temperatures up to 80° C.

These extended release particles are blended with the immediate release particles and tested by a USP XXII method with the following results:

PSEUDOEPHEDRINE HYDROCHLORIDE 240 mg/CHLORPHENIRAMINE MALEATE 24 mg EXTENDED-RELEASE CAPSULE	
Composition	%
Pseudoephedrine Hydrochloride, USP	44.04
Chlorpheniramine Maleate, USP	4.40
Sugar Spheres, NF	22.01
Talc, USP	9.86
Calcium Stearate, NF	8.61
Povidone, USP	1.57
Ethylcellulose, NF	2.84
Diethyl Phthalate, NF	0.06
Sugar Spheres, NF-QS	6.61
	100.00

The pseudoephedrine hydrochloride and chlorpheniramine maleate are pulverized and then blended together and applied to the sugar spheres using 0.178 cc/capsule of a 10% povidone solution in isopropyl alcohol.

The so prepared particles are dried to remove the solvents at temperatures up to 80° C.

To these dried particles, an inert seal coat of 38.1 mg of talc with 0.021 cc/capsule of a 10% povidone solution in isopropyl alcohol is applied. After the inert seal is applied, the particles are dried again to remove any residual solvents at varying temperatures up to 80° C.

To the above particles the diffusion control membrane is applied. The solution of this membrane is composed of 5% ethylcellulose with 0.1% diethyl phthalate in a co-solvent system composed of 2 parts of isopropyl alcohol and 1 part methylene chloride, applied with 15.65 mg of talc and the calcium stearate. The so prepared particles are dried to remove any residual solvents at temperatures up to 80° C.

These extended release particles are blended with the immediate release particles and tested as previously described.

DISSOLUTION RESULTS OF EXAMPLE 2

Time (h)	Pseudoephedrine Hydrochloride % Released	Chlorpheniramine Maleate % of release
1	25	24
4	39	42
8	69	68
12	84	80
24	96	90

Potassium Chloride 10 mEq Extended-Release Capsule	
Composition	%
Potassium Chloride, USP	77.72
Talc, USP	7.77
Ethylcellulose, NF	2.81
Dibutyl Sebacate	0.02
Diethyl Phthalate, NF	0.04
Calcium Stearate, NF	6.27
Sugar Spheres, NF	5.37
	100.00

Talc is applied onto the potassium chloride crystals using 0.213 cc/capsule of a solution composed of 5% w/w ethylcellulose with 0.1% w/w dibutyl sebacate dissolved in 34.9% w/w methylene chloride, and 60.0% w/w isopropyl alcohol.

The so-prepared particles are dried to remove the residual solvents at temperatures up to 80° C.

To these dried particles, the diffusion control membrane is applied. The solution of this membran is composed of 5% w/w ethylcellulose with 0.1% w/w diethyl phthalate, in a co-solvent system composed of 2 parts isopropyl alcohol and 1 part methylene chloride, applied with 61 mg. of calcium stearate. The so-prepared particles are dried to remove any residual solvents at temperatures up to 80° C.

These extended-release particles may be blended with the immediate release particles and tested for dissolution with the following results:

Dissolution Results Example	
Time (h)	% of Release
1	5
8	34
16	58
24	75
	Range of Dissolution
Hour	
1	0-50%
8	20-70%
24	NLT 60%

Gastrointestinal Blood Loss

In one investigation for gastrointestinal irritation, 32 swine were used. In this study, the swine were sacrificed and the gastrointestinal track was examined. In the placebo and the potassium chloride capsules of this invention, no significant lesions were observed in the swine. Microscopic lesions were apparent in the animals treated With Slow-K^{R} tablets and Micro-K^{R} capsules.

Capsules produced by this invention were less irritating than these other commercially available potassium chloride controlled release preparations at comparable dose levels. See Example 6.

EXAMPLE 5

to demonstrate maximum safety, the product by this invention was dosed at four times the level of potassium chloride as the commercial products tested per dosing interval, yet indicating significant reduction in gastrointestinal irritation.

Human Studies

A. EXPERIMENTAL DESIGN/METHODS

The effect on gastrointestinal blood loss of orally administered inventive potassium chloride capsules, Micro-K^{R} capsules, Slow-K^{R} tablets, aspirin and placebo was investigated in a study on humans.

The subjects were 40 healthy caucasian males; they ranged in age from 18-55 years. On the basis of a history and laboratory and physical examinations performed within two weeks of study initiation, it was concluded that all subjects met all study admission criteria.

The subjects were sequestered for the duration of the study, and a parallel design was employed. During two treatment periods (each seven days long, the first of which was preceded by a three-day period during which treatment was withheld), the subjects received appropriate daily oral doses of placebo and then one of the test drugs. Each subject collected his 24-hour stool sample and delivered the samples to laboratory personnel each day. Blood samples were obtained from each subject at weekly intervals. The subjects were provided with a standardized diet, were told not to use drugs other than those dispensed to them by laboratory personnel, and were given a soft toothbrush.

B. RESULTS AND CONCLUSIONS

Thirty-eight of the 40 subjects completed the study as scheduled; two of the subjects left the study site early, on study day 18 (after providing the scheduled blood sample). Daily fecal blood volumes averaged 0.28 and 0.52, 0.28 and 0.50, 0.36 and 0.54, and 0.40 and 6.63 ml during periods of treatment with placebo and inventive potassium chloride capsules, placebo and Slow-K^{R} tablets, placebo and Micro-K^{R} capsules, and placebo and aspirin, respectively. The results observed during periods of treatment with aspirin validate the methodology.

Statistical analysis revealed that the average daily fecal blood volumes observed during periods of treatment with placebo did not differ from each other, that the average daily fecal blood volumes observed during periods of treatment with the three potassium chloride formulations did not differ from each other (despite the fact that the fractional doses of Micro-K^{R} capsules and Slow-K^{R} tablets were less than one-fourth the once daily dose of inventive potassium chloride capsules), and that the differences between the average daily fecal blood volumes observed during periods of treatment with placebo and the three potassium chloride formulations did not differ from each other. These results indicate that the greater patient compliance, which can be expected to result from the once daily dosing with inventive potassium chloride capsules, will not come at the cost of increased gastrointestinal toxicity.

EXAMPLE 8

Capsule Composition	Wt. Per Capsule
Nitroglycerin Triturate	10% 250.0 mg
Silicon Dioxide	5.5 mg
Calcium Stearate	37.1 mg
Ethylcellulose	6.8 mg
Sugar Spheres	34.7 mg
Diethyl Phthalate	0.1 mg
Talc	65.6 mg
Povidone	15.8 mg

The nitroglycerin triturate is blended with the silicon dioxide and applied on the sugar spheres using 0.109 cc per capsule of a 10% povidone solution in isopropanol.

The prepared particles are then dried to remove the solvents at temperatures up to 80° C.

To these dried particles, a release coating of 30 mg of talc with 0.0125 cc per capsule of a 13% povidone solution in isopropanol is applied. After the coating is applied, the particles are dried again to remove any residual solvents at varying temperatures up to 80° C.

To the above particles the controlled-release layer is applied. The solution of this layer is composed of 5% ethylcellulose with 0.1% diethyl phthalate in a co-solvent system composed of two parts of isopropanol and one part methylene chloride, applied with 35.6 mg of talc and the calcium stearate. The product is then dried to remove any residual solvents at temperatures up to 80° C.

The finished product was then subjected to dissolution testing.

Dissolution Results of Example 8

Release Method Bottle	Time (h)	% Release USP Rev.
	1	79
	12	2223
	24	6765

As shown in Figs. and 2, the original drug dose maintains its effectiveness after twenty-eight days of daily therapy. Therefore, pharmacologic tolerance, observed in other formulations of long-acting nitrates and resulting in a requirement for increasingly higher doses of drug to obtain the same pharmacologic effect, does not occur with this formulation in this time period.

More particularly, the graph in Fig. 1 depicts 28 days of administration of optimum doses of the organic nitrate formulation according to the present example (KV/24 controlled-release nitroglycerin), and 28 days of placebo, crossing over in a randomly determined sequence. The dosing periods were separated by a 4-7 day washout. The 20 patients were subjected to treadmill testing before and at 12 hours, 16 hours, and 24 hours after the first and last daily doses in each period. In the treadmill test depicted in Fig. 1, the time to onset of chest pain is measured, and in the treadmill test depicted in Fig. 2, the ability to continue

EXAMPLE 10

Composition	Wt. Per Capsule
Isosorbide 5-Mononitrate (50% Triturate)	160.0 mg
Sugar Spheres	61.0 mg
Talc	46.0 mg
Povidone	2.7 mg
Calcium Stearate	8.6 mg
Pharmaceutical Glaze	14.0 mg
Diethyl Phthalate	0.2 mg
Ethylcellulose	9.4 mg

The isosorbide 5-mononitrate (IS-5-MN) triturate is applied on sugar spheres by means of 0.176 cc per capsule of the pharmaceutical glaze and the povidone solution.

The so prepared particles are dried to remove the solvents at temperatures up to 80° C.

To these particles a coating of talc is applied using 0.507 cc per capsule of polyvinyl chloride and pharmaceutical glaze. After the coating is applied, the particles are dried again to remove any residual solvents at varying temperatures up to 80° C.

To the above particles, the controlled-release layer is applied. The solution of this layer is composed of 5% ethylcellulose, diethyl phthalate 0.1% in a co-solvent system composed of equal parts of isopropanol and methylene chloride, applied with talc and calcium stearate. The so prepared particles are then dried to remove any residual solvents at temperatures up to 80° C.

The product was then subjected to dissolution testing by the USP XXI Apparatus II (paddle) in a 7.5 pH phosphate buffer.

Dissolution Results of Example 10

Time (h)	Found
1	5%
4	35%
12	70%

group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, metal salts, minerals, vitamins and mixtures thereof.

3. The extended release pharmaceutical formulation of claim 1, wherein the inert spherical substrate particles are selected from the group consisting of sugar spheres and non- toxic plastic resin beads.

4. The extended release pharmaceutical formulation of claim 1, which additionally contains preblended with the drug a non-toxic carrier selected from the group consisting of sugar, lactose, gelatin, starch, silicon dioxide and mixtures thereof.

5. The extended release pharmaceutical formulation of claim 1 wherein the binder is soluble in a solvent selected from water and an organic solvent.

6. The formulation of claim 5, wherein the binder is selected from the group consisting of povidone, pharmaceutical glaze, sugar, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, acrylic and methacrylic acid co-polymers and mixtures thereof.

7. The extended release pharmaceutical formulation of claim 1 wherein the plasticizers which are used to form the extended release particle are selected from the group consisting of diethyl phthalate, diethyl sebacate, triethyl citrate, crotonic acid, propylene glycol, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate and mixtures thereof.

8. The extended release pharmaceutical formulation of claim 1 wherein the film forming agent is selected from the group consisting of ethylcellulose, methylcellulose, hydroxypropylcellulose, cellulose acetate, hydroxypropylmethylcellulose, hydroxyethylcellulose and mixtures thereof.

9. The extended release pharmaceutical formulation of claim 1 wherein the immediate release particle contains a core comprising about 15 to about 40% inert spherical substrate particles, about 0.5 to about 4% binder and about 4 to about 85% drug, all percents herein are by weight of the final product.

10. The formulation of claim 9, wherein the particle comprises about 4 to 20% talc coating.

11. The extended release pharmaceutical formulation of claim 1, wherein the extended release particle contains the coated immediate release particle in amounts of about 65% to about 95% by weight and remaining amount of coating of about 5.0 to about 35% by weight.

12. The formulation of claim 11, wherein the coating over the immediate release particle contains about 0.5 to about 25% film forming agent by weight, about 0.01 to about 5% plasticizer by weight, and up to 25% of modifying agents.

13. The controlled release granule of claim 11, wherein the coating of the immediate release particles contains additional amounts of drug.

14. The extended release pharmaceutical formulation of claim 1, wherein the formulation is administered in the form of a tablet, capsule or oral solid particle dosage form.

15. The extended release pharmaceutical formulation of claim 1, wherein the drug is pseudoephedrine hydrochloride.

16. The extended release pharmaceutical formulation of claim 1, wherein the drug is pseudoephedrine hydrochloride and chlorpheniramine maleate.

17. The extended release pharmaceutical formulation of claim 1, wherein the drug is pseudoephedrine hydrochloride and triprolidine.

18. The extended release pharmaceutical formulation of claim 1, wherein the drug is phenylpropanolamine hydrochloride and chlorpheniramine maleate.

19. The extended release pharmaceutical formulation of claim 1 wherein the drug is an organic nitrate.

20. The extended release pharmaceutical formulation of claim 1 which comprises an organic nitrate formulation for once-per-day oral administration which achieves a therapeutically effective level of the organic nitrate, while effecting a drug holiday towards a latter portion of the daily dosing period so as not to induce tolerance.

21. The organic nitrate formulation according to claim 20, wherein said organic nitrate is selected from the group consisting of nitroglycerin, isosorbide 5-mononitrate, isosorbide dinitrate, and mixtures thereof.

22. The controlled-release organic nitrate formulation according to claim 21, wherein said nitroglycerin comprises a nitroglycerin triturate.

23. The organic nitrate formulation according to claim 21, wherein said nitroglycerin triturate includes 1-20 percent by weight nitroglycerin.

24. The organic nitrate formulation according to claim 22, wherein said rate of release of the organic nitrate is substantially equivalent to a rate of release of the organic nitrate as measured in vitro in a basket assembly according to U.S. Pharmacopoeia XXI, wherein less than 30% of the organic nitrate is released after 1 hour of measurement, less than 40% of the organic nitrate is released after 12 hours of measurement, and less than 90% of the organic nitrate is released after 24 hours of measurement.

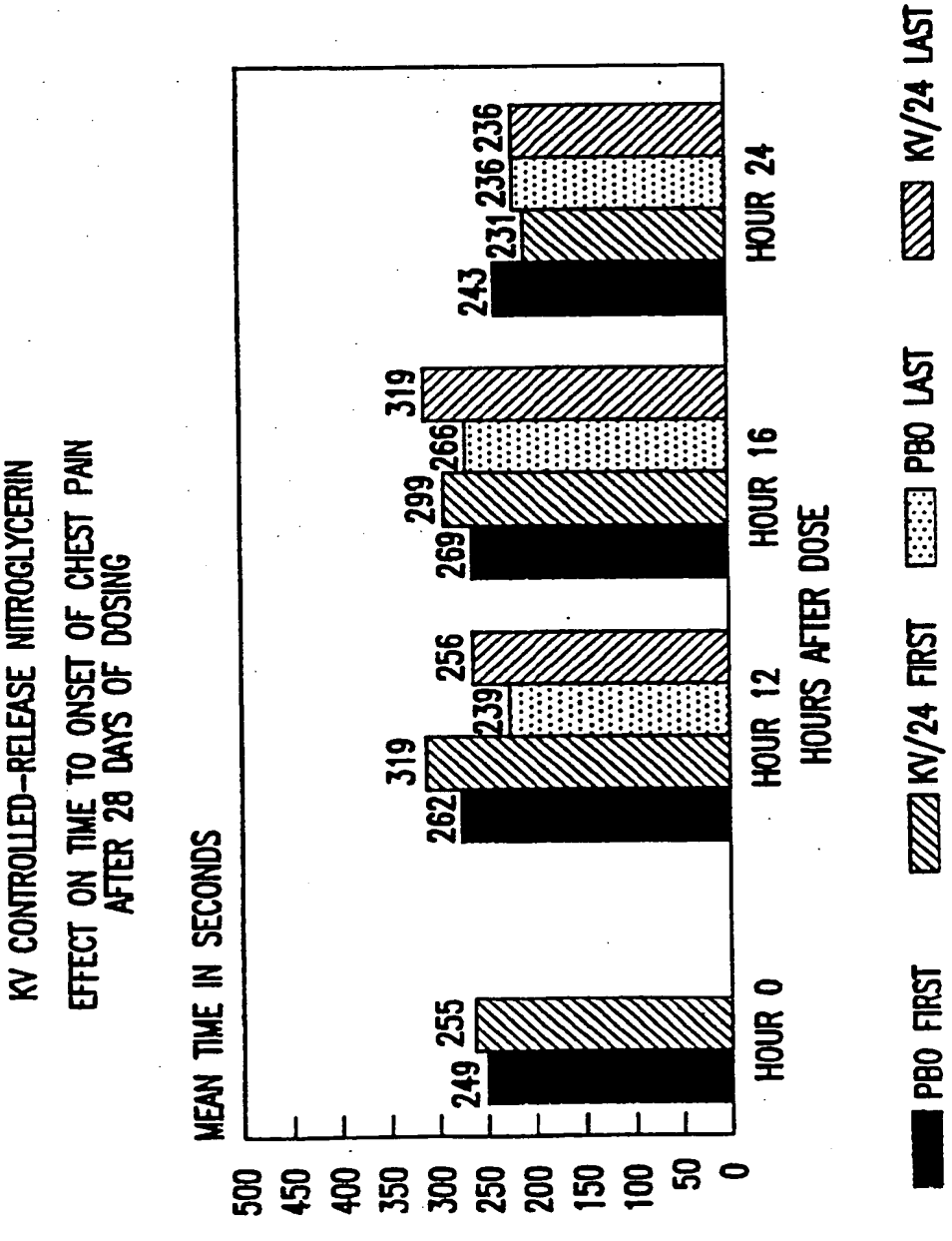

FIG. 1